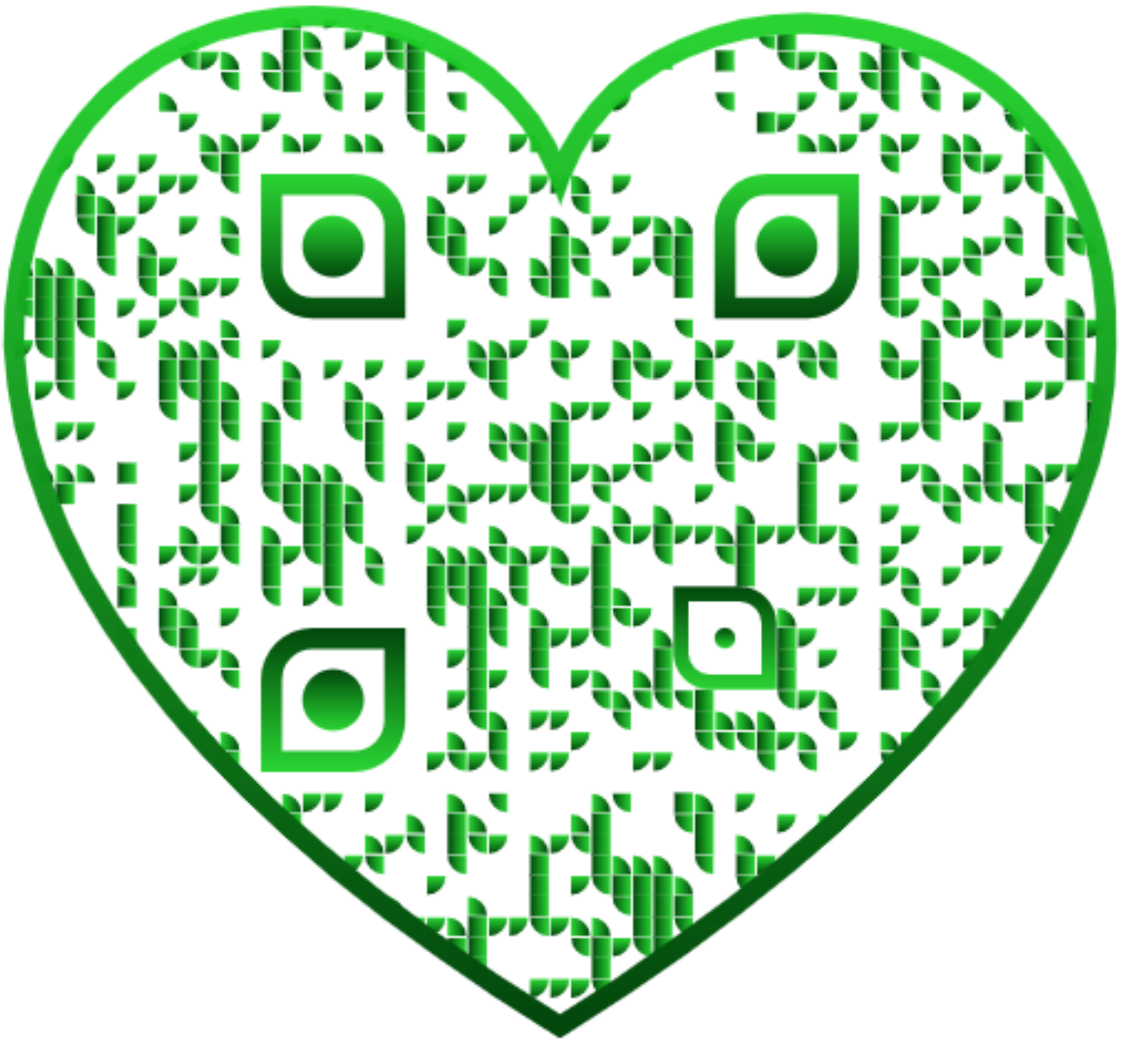
9. Pharmaceutical Suspensions



Introduction

- Disperse systems?
- Classification based on particle size?
- The theory and technology of interfacial and colloidal principles, micromeritics, and rheology,
- The term "Disperse System" refers to a system in which one substance (the dispersed phase) is distributed, in discrete units, throughout a second substance (the continuous phase).

- Suspensions (Definitions)
  - A coarse dispersion in which insoluble solid particles are dispersed in a liquid medium,
  - Finely divided solid is dispersed uniformly in a liquid dispersion medium,
  - The disperse phase consisting of insoluble solid particles having a range of size (0.5 to 5 microns)
  - The suspension is known as pharmaceutical suspension, when the dispersed phase is therapeutically active,

- Physical characteristics of a suspension depend on their intended route of delivery.
- Oral suspensions generally have high viscosity and may contain high amounts of dispersed solid.
- A parenteral suspension on the other hand usually has low viscosity and contains less than 5% solids.

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- Many drug formulations are available as suspensions:
  - Oral antacid suspensions
  - Oral antibacterial suspensions
  - Oral analgesic suspensions
  - Oral anthelmintic suspensions
  - Oral anticonvulsant suspensions
  - Oral antifungal suspensions
  - Dry antibiotic powders for oral suspensions
  - Intramuscular antidiarrheal suspensions
  - Intravenous anticancer suspensions
  - Intramuscular contraceptive suspensions
  - Topical lotions for various skin conditions

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- Why we formulate suspensions:
  - If the drug is insoluble in the delivery vehicle, and liquid form is preferred,
  - Flexibility in administration of a range of doses (for liquid DFs),
  - To mask the bitter taste of the drug,
  - To increase drug stability (if chemically unstable in solution),
  - To achieve controlled/sustained drug release (IM depot therapy),
  - Avoidance of the use of cosolvents,

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- Desirable qualities of Pharmaceutical Suspensions:
  - The suspended material should not settle rapidly,
  - Settled particles to the bottom must not form a hard cake,
  - Should be readily redispersed upon shaking,
  - Must not be too viscous,
  - Must have an acceptable color and odor.
  - For external use: acceptable rheological characteristics.

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- Some physicochemical consideration to formulate stable suspension:
  - Particle-size distribution,
  - Specific surface area,
  - Crystal growth,
  - Polymorphic form.

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- Physical stability of suspensions may be defined as the condition in which:
  - particles do not aggregate,
  - they remain uniformly distributed throughout the dispersion,
  - if the particles do settle, they should be easily resuspended by a moderate amount of agitation.

Interfacial Properties of Suspended Particles

- Energy conditions at the surfaces of solids must be known for the successful stabilization of suspended particles,
- Size must be reduced to disperse them in a continuous medium,
- This is associated with an increase in SA, which results in an increase in surface free energy that makes the system thermodynamically unstable.

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- Particles with reduced size are highly energetic and tend to regroup in such a way as to decrease the total area and reduce the surface free energy.
  - Tend to flocculate (fluffy conglomerates held by van de Waals forces), or
  - Tend to aggregate and form cake (held by stronger forces)

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- The surface free energy, ΔG, due to an increasing the total surface area, ΔA, is given by:

$$\Delta G = \gamma_{LS} \times \Delta A$$

  - To approach a stable state, the system tends to reduce ΔG by:
    - Reducing the interfacial tension
    - Which in turn is achieved by a decrease of the interfacial area (which leading to flocculation or aggregation – desirable or undesirable?)

Electrical properties of Suspended particles

- Properties related to charged surfaces (in relation to their liquid surfaces)
- Particles may become charged either:
  - By selective adsorption of a particular ionic species,
  - From ionization of groups (such as COOH) that may be situated at the surface of the particle,
  - When there is a difference in dielectric constant between the particle and its dispersion medium (less common).

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a) Electric Double Layer (EDL)

- Assume a solid surface in contact with a polar solution containing ions,
- And, let some of the cations are adsorbed onto the surface (being positively charged),
- Remaining in solution are the rest of the cations plus the total number of anions,
- The anions are attracted to the positively charged surface by electric forces, while cations are repelled,
- In addition to these electric forces, thermal motion tends to produce an equal distribution of all the ions in solution,

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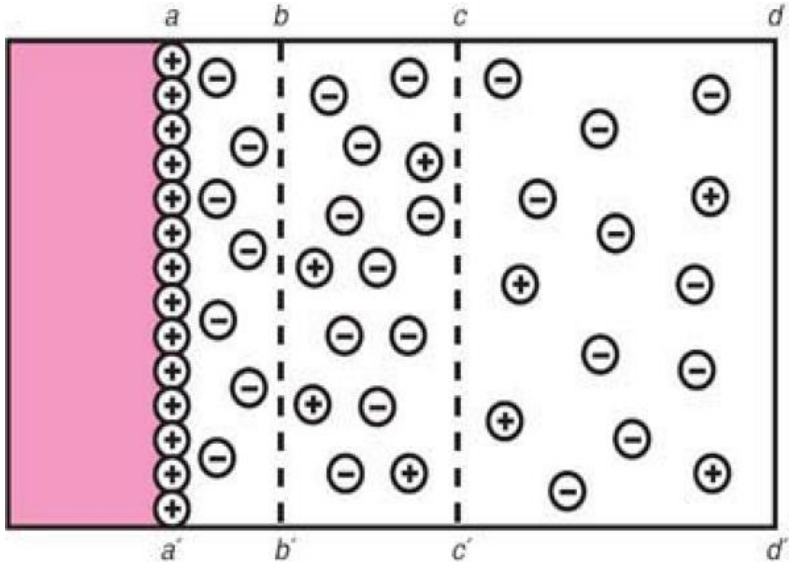
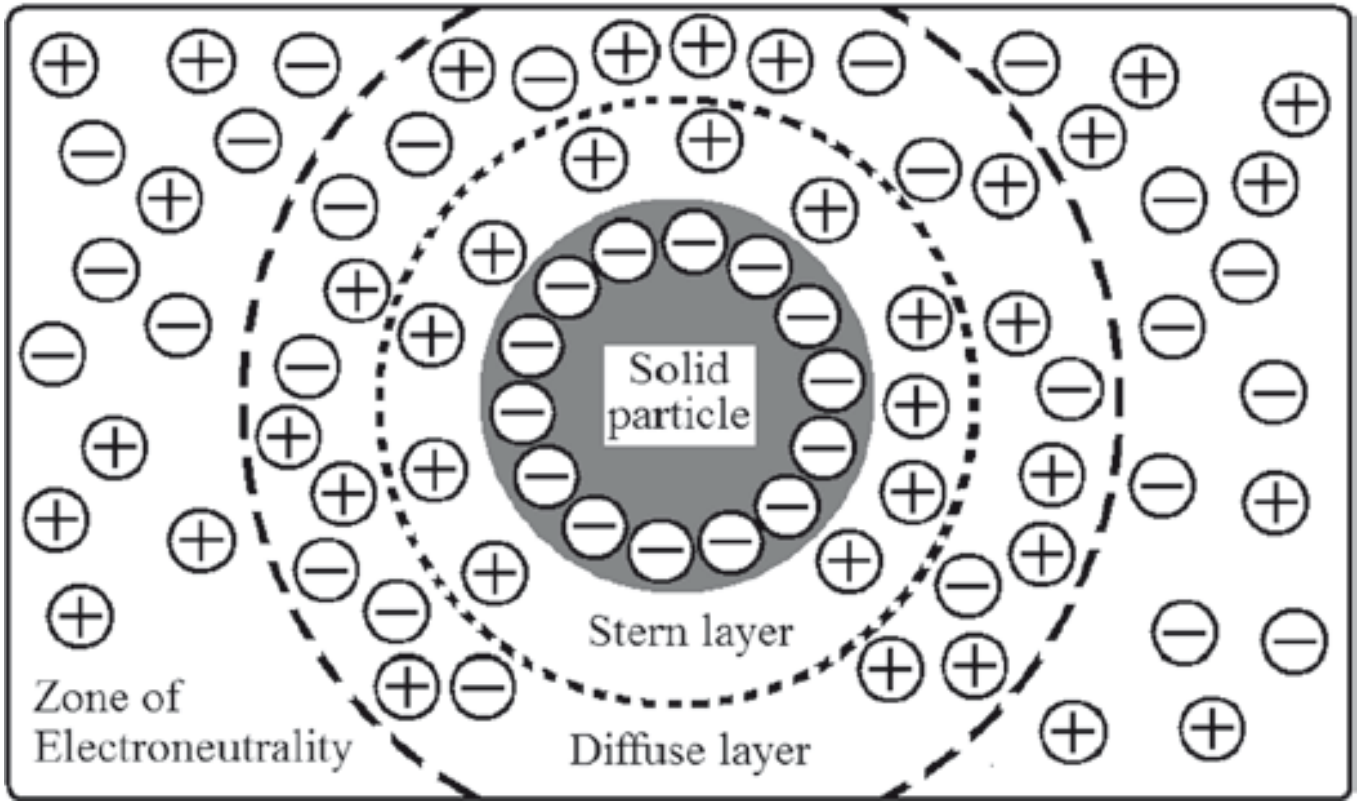
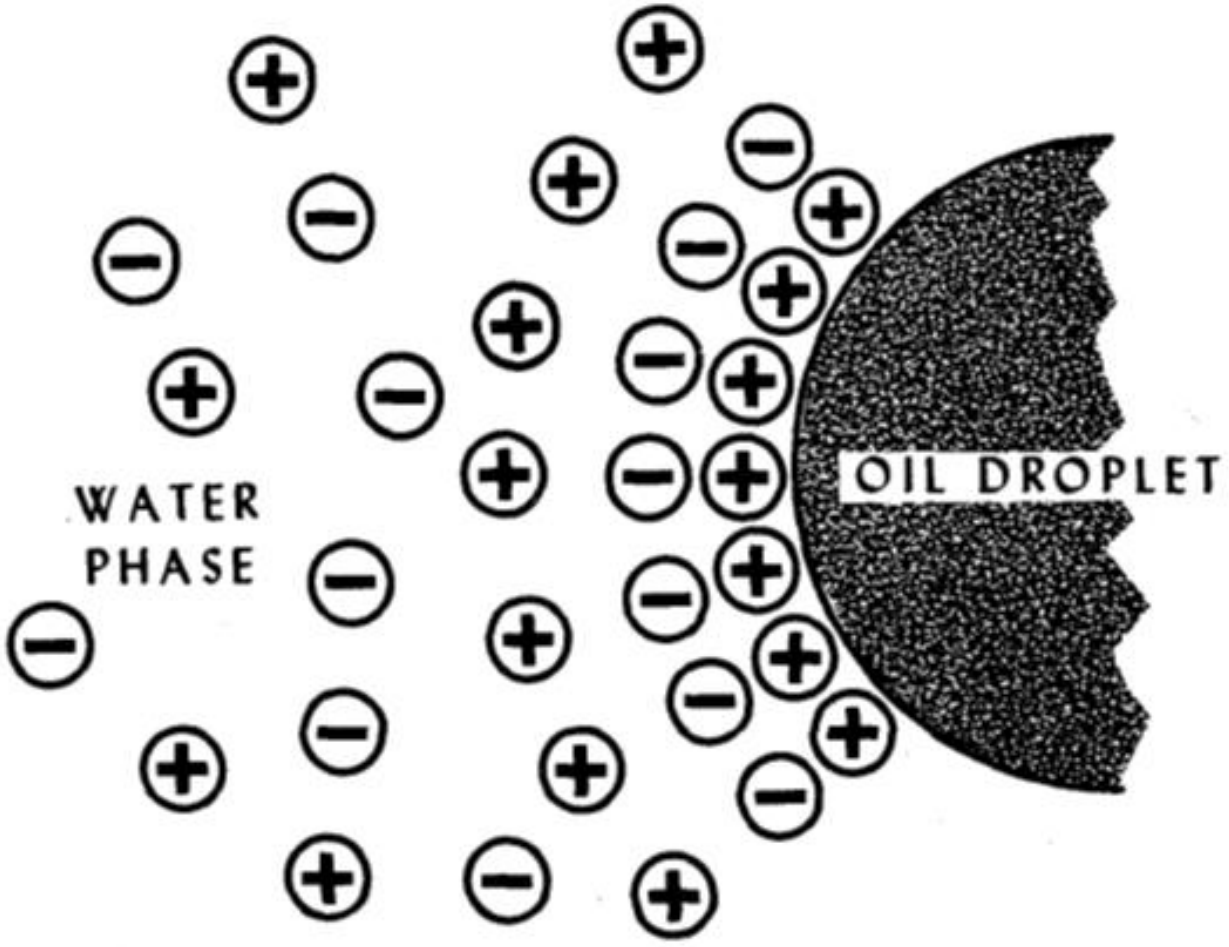
- At a particular distance from the surface, the concentrations of anions and cations are equal (electric neutrality),
- The adsorbed ions that give the surface its charge are referred to as the potential-determining ions,
- The ions having a charge opposite to that of the potential-determining ions are known as counter-ions or gegen-ions,



- The electric distribution at the interface is equivalent to a double layer of charge
- Region $\overline{aa}$ to $\overline{bb}$ ~ is called tightly bound layer
- Region $\overline{bb}$ to $\overline{cc}$ ~ is called diffuse layer
  - There is an excess of negative ions
- $\overline{bb}$ ~ is called shear plane,
  - May be assumed as the true surface rather than $\overline{aa}$
  - The potential is still positive?
- Beyond $\overline{cc}$ ~ distribution of ions is uniform and electric neutrality is obtained


Solid particle
Stern layer
Zone of Electroneutrality
Diffuse layer


WATER
PHASE
OIL DROPLET

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- Two other situations:

1) If the counter-ions in the tightly bound (solvated) layer equal the positive charge on the solid surface,

   - Then, electric neutrality occurs at the plane $\overline{bb}$ rather than $\overline{cc}$.

2) If the total charge of the counter-ions in the tightly bound region exceed the charge on the solid surface,

   - Then, the net charge at $\overline{bb}$ will be negative rather than positive.

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b) Nernst and Zeta Potentials

- There is a change in electric potential with distance from the surface,
- The potential at the solid surface due to the potential-determining ion is the electro-thermodynamic (Nernst, E) potential,
  - It is the difference in potential between the actual surface and the electro-neutral region of the solution.

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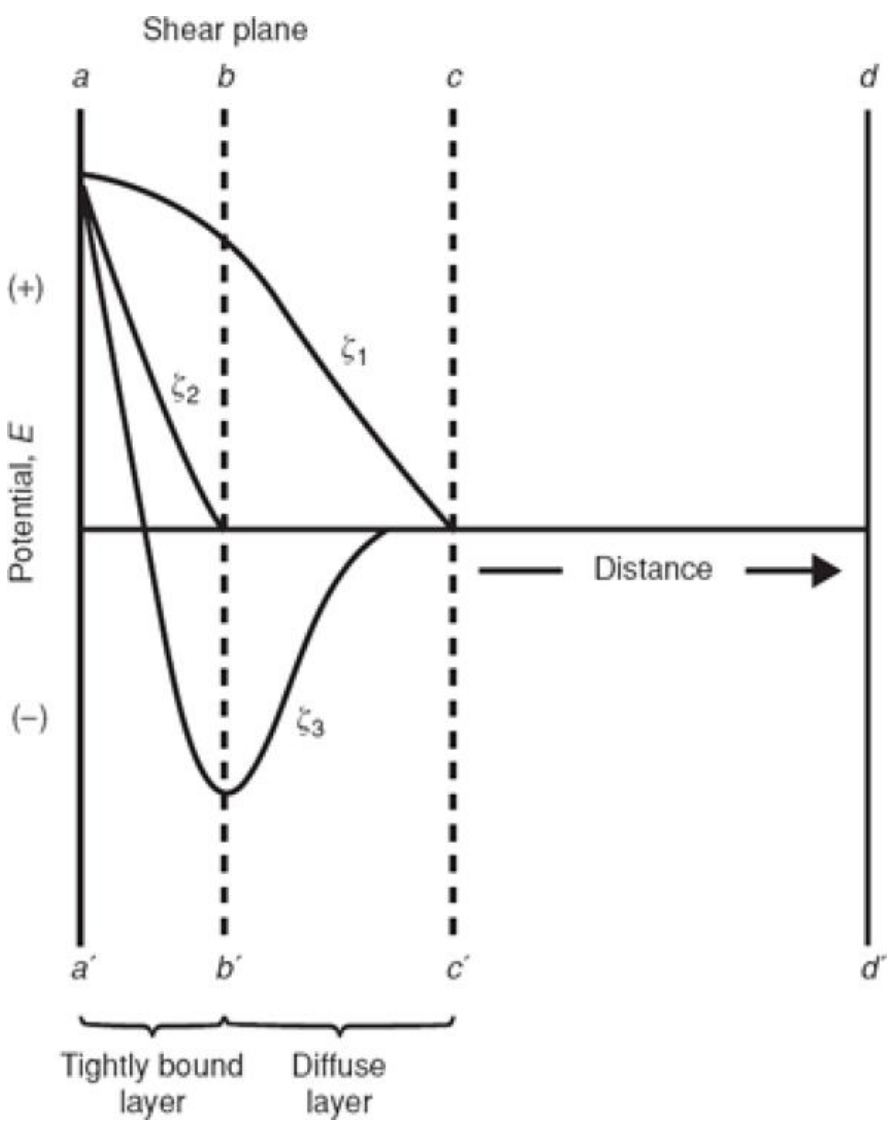
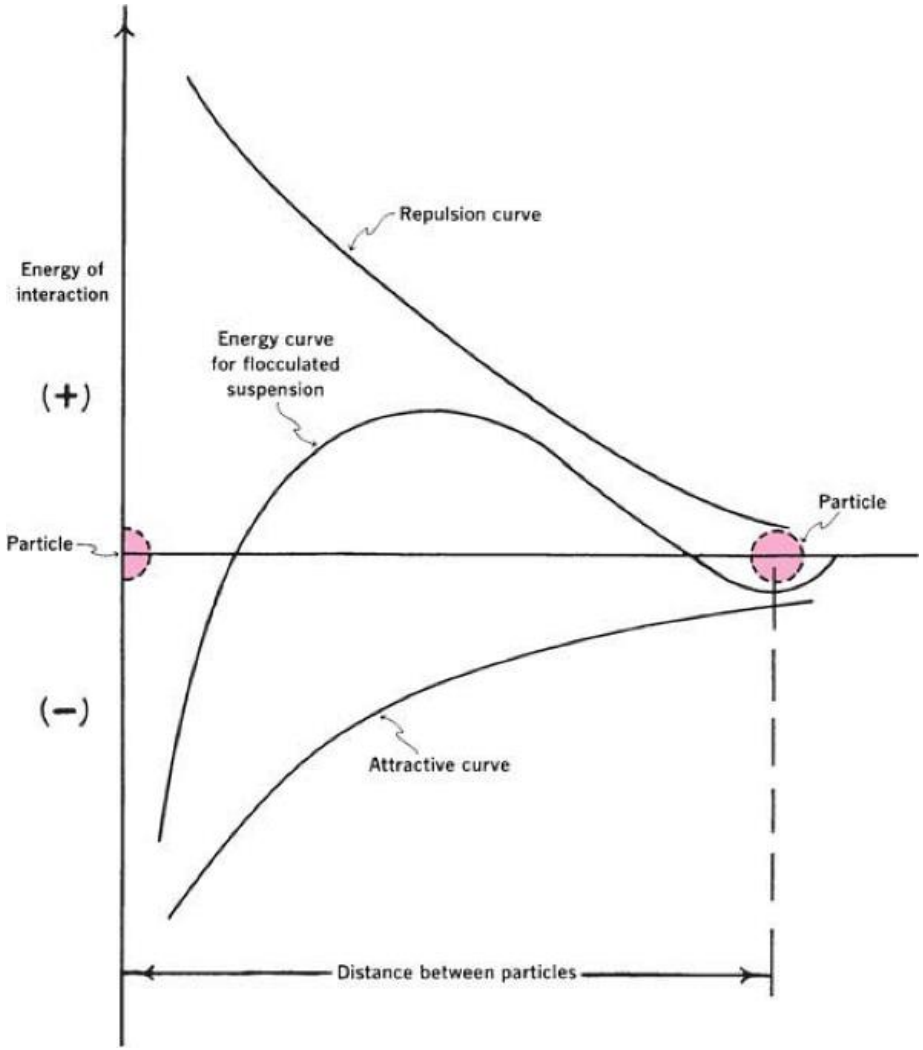
- The potential located at the shear plane is known as the electro-kinetic (zeta potential, ζ),
  - It is the difference in potential between the surface of the tightly bound layer (shear plane) and the electro-neutral region.



- The zeta potential initially drops off rapidly, followed by a more gradual decrease with distance from the surface,
- Although E is the same in all three cases, the zeta potentials are positive (ζ1), zero (ζ2), and negative (ζ3),
- The zeta potential has practical application in the stability of systems containing dispersed particles,
  - It governs the degree of repulsion between adjacent, similarly charged, dispersed particles.
  - If it is reduced below a certain value, the attractive forces exceed the repulsive forces, and the particles come together.



- **Fig**. Potential energy curves for particle interactions in suspension.
- When the repulsion energy is high, the potential barrier is also high, and collision of the particles is opposed.
- The system remains deflocculated,
  - When sedimentation is complete, the particles form a close-packed arrangement,
  - The smaller particles filling the voids between the larger ones,
  - Particles lowest in the sediment are gradually pressed together by the weight of the ones above,
  - The energy barrier is thus overcome, allowing the particles to come into close contact (forming a cake & difficult to redisperse)

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c) DLVO Theory

- Particles in suspension may be in continuous collision, due to:
  - Brownian motion or
  - Differential sedimentation rates
- This may result in formation of aggregates or redispersion of the particles,
- The outcome of collision depends on the attractive or repulsive forces between the particles.

- The zeta potential plays a very important role in suspension stability.
- Adding electrolytes can reduce zeta potential and may results in precipitation,
- The precipitating power of electrolytes increases rapidly with the valence of the ions (Schulze-Hardy rule).
- (Derjaguin and Landau) and (Verwey and Overbeek) worked independently and used the Schulze-Hardy rule to describe the stability of lyophobic colloids.

- According to DLVO theory,
  - The potential energy of interaction between particles, V_T is the result of repulsion due to EDL, V_R and attraction due to van der Waals' force, V_A

$$V_T = V_R + V_A$$

  - V_T is calculated by subtracting the smaller value from the larger one,
    - When the net energy curve remains above the baseline, it represents repulsion, and vice versa.
    - The maximum repulsive value is known as the energy barrier.

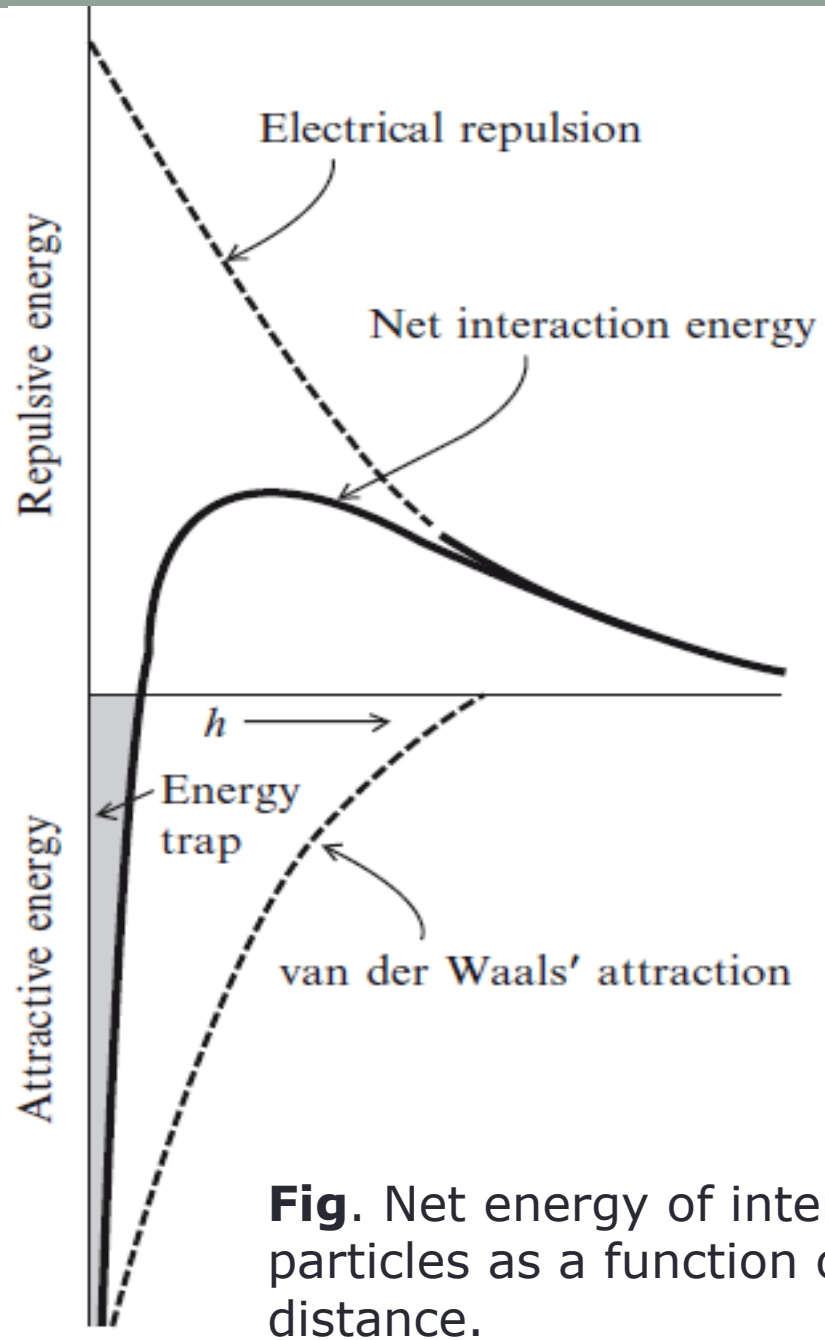

Fig. Net energy of interaction between two particles as a function of interparticulate distance.

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d) Effect of Electrolytes

- Electrolytes may increase the screening effect of the counter-ions.
- This may decrease zeta potential more rapidly with distance
  - This is due to shrinking of the double layer.
- A similar situation occurs when the valency of the counter-ion is increased.

Sedimentation in Suspensions

Stokes's law

$$v = \frac{2r^2(\rho - \rho_0)g}{9\eta_0}$$

- This equations holds true (for free settling) for:
  - Dilute suspensions (usually 0.5% to 2.0% (w/v) preparations),
  - Spherical particles of about 0.5 µm.

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- Most pharmaceutical suspensions contain dispersed particles in concentrations of 5%, 10%, or higher percentages,
  - Where the particles exhibit hindered settling,
  - The particles interfere with one another as they fall, and Stokes's law no longer applies,
  - Moreover, the particles in pharmaceutical suspensions show non-uniformity in particle shape and size.
    - To account for such non-uniformity, we use modified Stokes's equation:

$$v' = v\varepsilon^n$$

v' ~ rate of fall at the interface
v ~ rate of fall at Stokes's law
ε ~ initial porosity of the system
n ~ measure of hindering (cons.)

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Effect of Brownian Movement

Sedimentation of Flocculated vs Deflocculated Particles

- In flocculated systems,
  - Flocs tend to fall together, producing a distinct boundary between the sediment and the supernatant liquid (clear).
- In deflocculated suspensions,
  - The larger particles settle more rapidly than the smaller particles, and no clear boundary is formed.
- Whether the supernatant liquid is clear or turbid during the initial stages of settling is a good indicator of the system.

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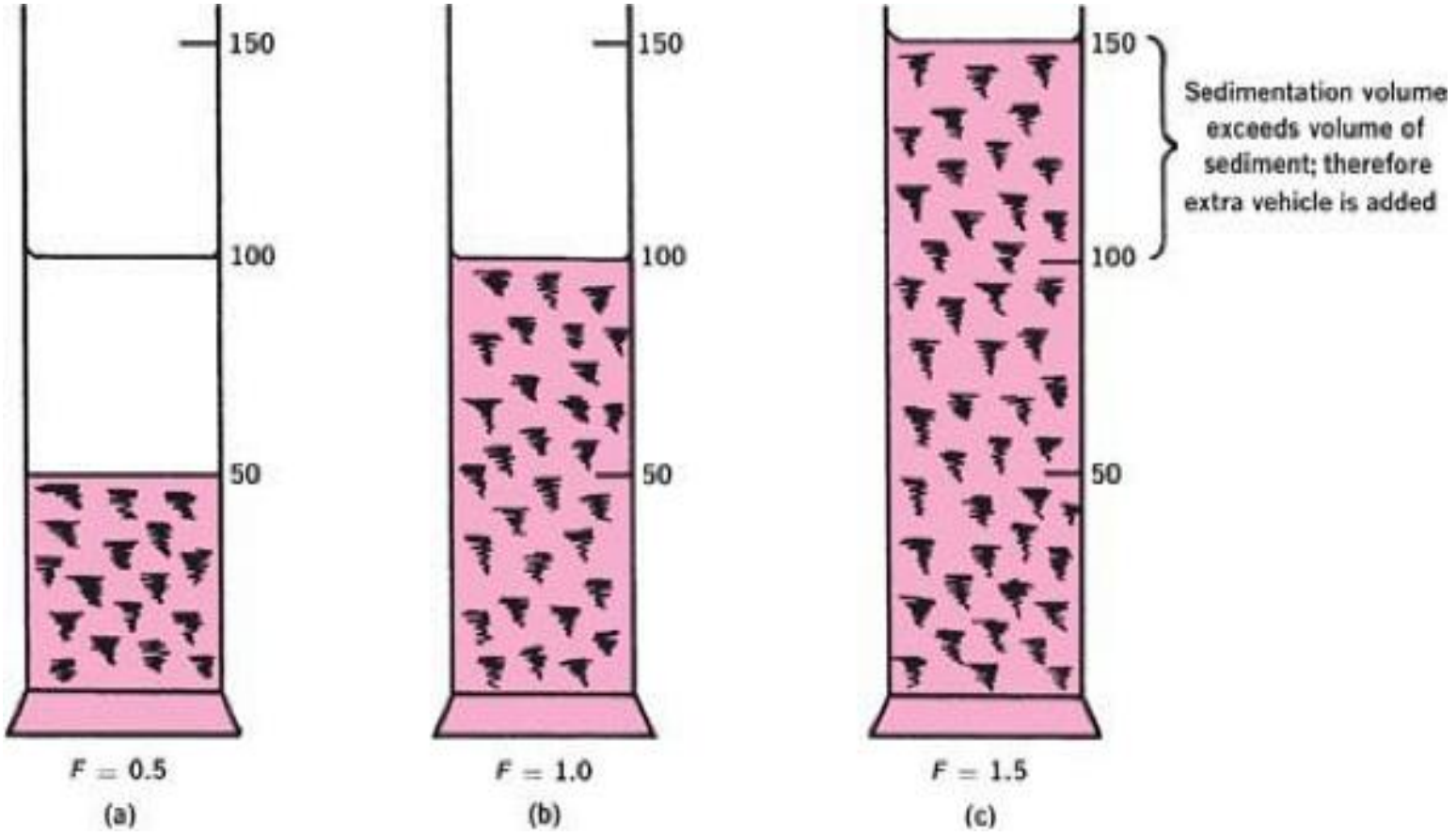
Sedimentation Parameters

a) Sedimentation volume (F):

$$F = \frac{V_u}{V_o}$$

- V_u - Volume of the sediment,
- V_o - Original volume of the suspension

- F will have values ranging from less than 1 to greater than 1,
- When,
  - F < 1
  - F = 1
  - F > 1


150
100
50
F = 0.5
(a)
150
100
50
F = 1.0
(b)
150
100
50
Sedimentation volume exceeds volume of sediment; therefore extra vehicle is added
F = 1.5
(c)

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b) Degree of flocculation (β):

- For a completely deflocculated suspension, the ultimate volume of the sediment will be relatively small,
- For such a system:

$$F_\infty = \frac{V_\infty}{V_o}$$

- The degree of flocculation (β) is given by the ratio of F to F_∞:

$$\beta = \frac{F}{F_\infty} = \frac{V_u}{V_\infty}$$

- V_u - ultimate sediment volume of flocculated suspension,
- V_∞- ultimate sediment volume of deflocculated suspension

Formulation of Suspensions

Formulation approaches

1) Using Structured vehicle,

   - To maintain deflocculated particles in suspension

2) Through controlled flocculation,

   - The application of the principles of flocculation to produce flocs

3) Combination of the above two

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1) Structured vehicles

- Structured vehicles are generally aqueous solutions of natural and synthetic polymers,
- Characterized by pseudoplastic and plastic flow (thixotropic)
- Act by entrapping the particles (generally deflocculated) so that, ideally, no settling occurs.
- In reality, some degree of sedimentation will usually take place.
- The "shear-thinning" property of these vehicles does, however, facilitate the re-formation of a uniform dispersion.

2) Controlled flocculation

- The problem with deflocculated systems is the formation of a compact cake when the particles eventually settle,
- Optimum physical stability and appearance will be obtained when the suspension is formulated with flocculated particles in a structured vehicle,
- The aim of controlled flocculation is to prevent formation of a compact sediment that is difficult to redisperse!!

- Flocculation can be produced in suspensions either by use of:
  - Electrolytes
  - Surfactants, and
  - Polymers

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- Electrolytes
  - Act as flocculating agents by reducing the electric barrier between the particles,
  - Their flocculating power increases with the valency of the ions,
  - Decreasing in the zeta potential and the formation of a bridge between adjacent particles,
  - This link particles together in a loosely arranged structure.

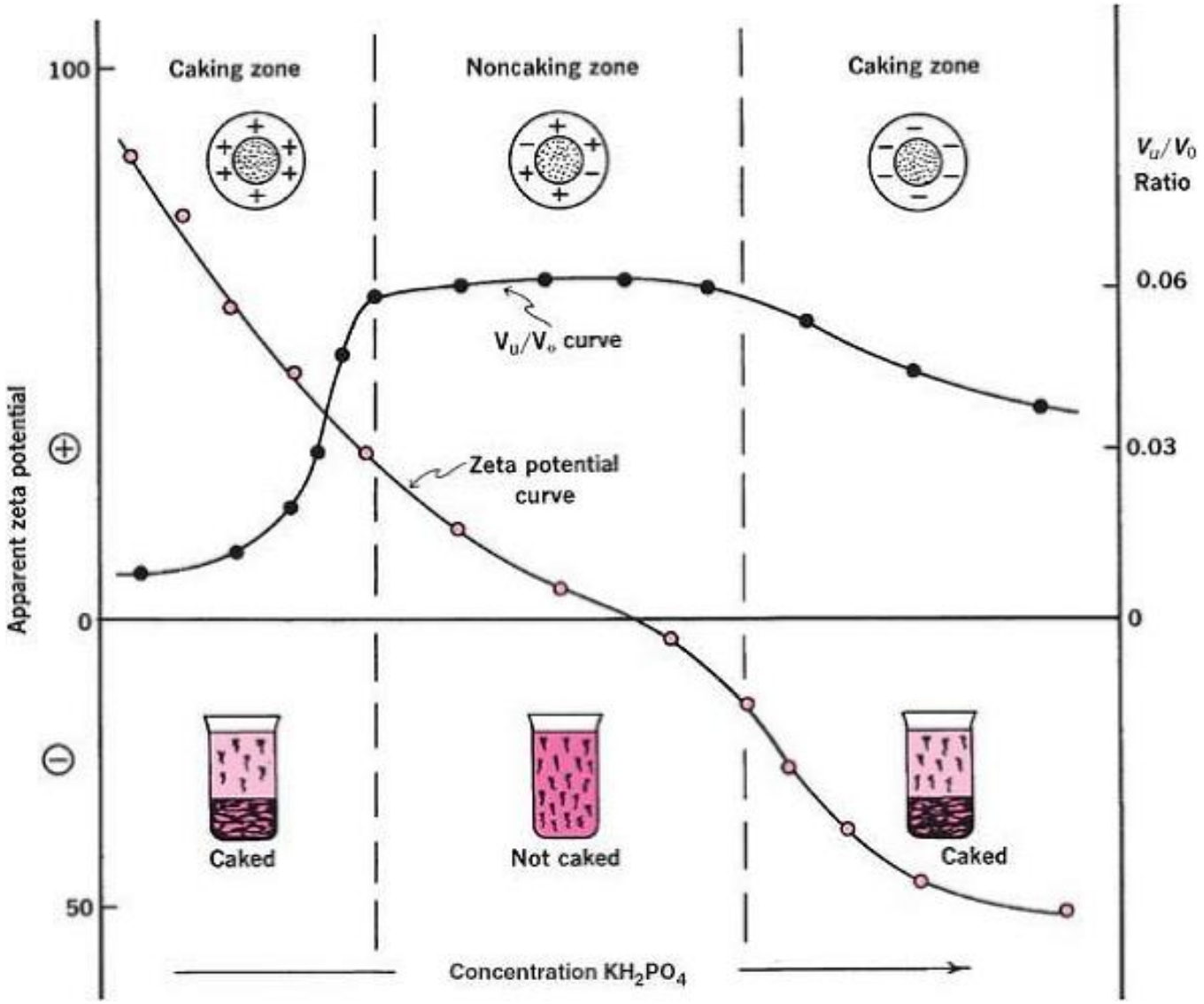


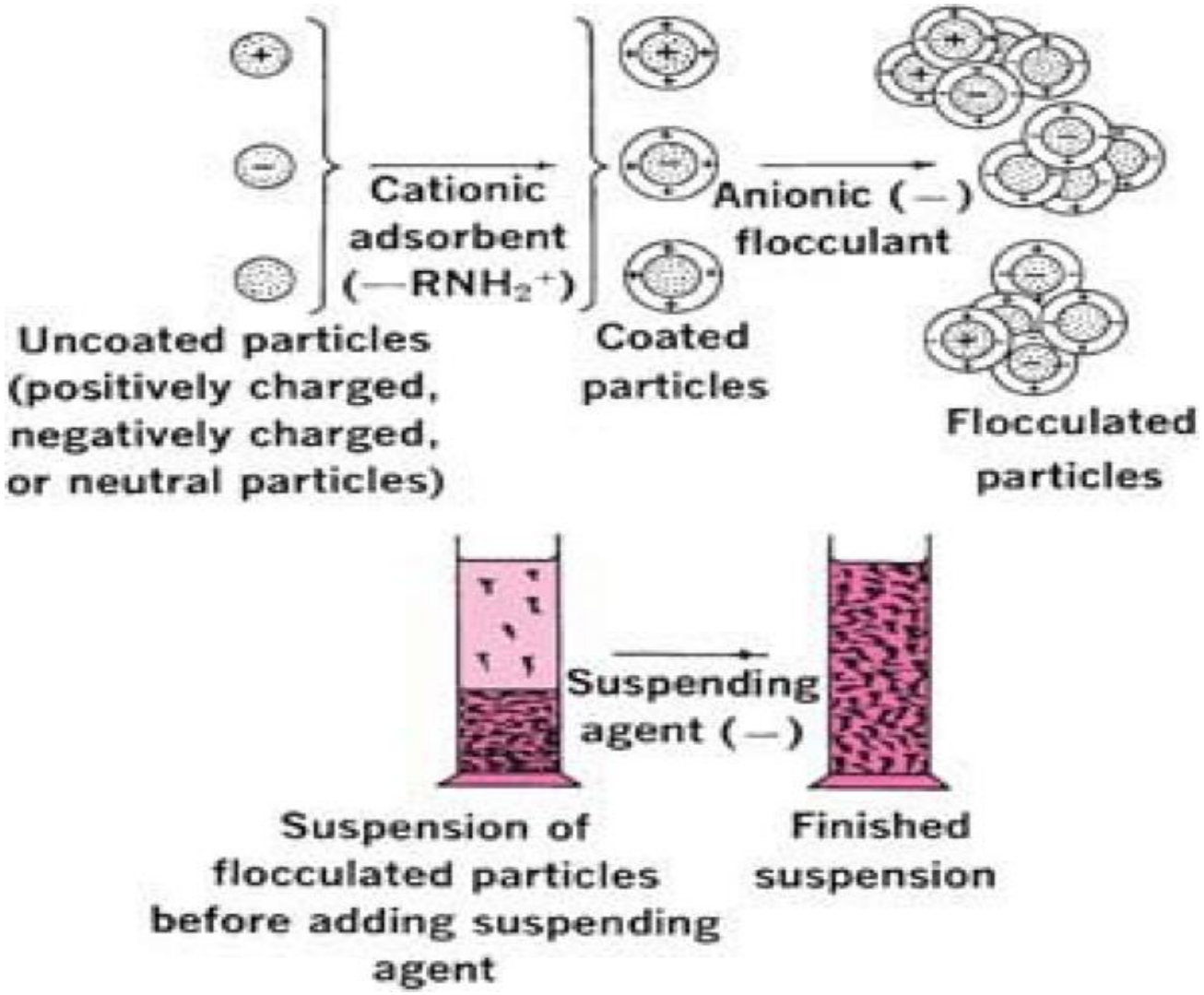
Fig. Caking diagram, showing the flocculation of a bismuth subnitrate suspension by means of the flocculating agent monobasic potassium phosphate.

- Surfactants
  - Both ionic and nonionic surfactants can be used as flocculating agents,
  - Ionic surfactants cause flocculation by neutralizing the charge on particles,
  - Because of long structure, nonionic surfactants are adsorbed onto more than one particle, thereby, forming a loose flocculated structure
  - Can also act as wetting and deflocculating agents to achieve dispersion.

- Polymers
  - Some polymers form a gel-like network that adsorbs onto the surface of dispersed particles, holding them in a flocculated state,
    - At concentrations, when the drug particles are not completely covered by the polymers,
  - Hydrophilic polymers can also function as protective colloids,
    - Flocs are sterically prevented from adhering to one another.
    - Loose sediment is the result.

3) Controlled Flocculation in Structured Vehicles

- Controlled flocculation is capable of providing the desired physical stability,
- But, product can look unsightly if "F" is not close or equal to 1,
- In practice, a suspending agent is frequently added to retard sedimentation of the flocs,
- However, this can lead to incompatibilities (due to charges on the particle, flocculating agent and suspending agent).
- It becomes necessary to use a protective colloid to change the charge on the particle.


Cationic adsorbent (—RNH2+)
Anionic (—) flocculant
Uncoated particles (positively charged, negatively charged, or neutral particles)
Coated particles
Flocculated particles
Suspending agent (—)
Suspension of flocculated particles before adding suspending agent
Finished suspension

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Rheological characteristics

- Rheologic principles can be applied to study:
  - Viscosity of a suspension as it affects the settling of dispersed particles,
  - Flow properties of the suspension when the container is shaken and when the product is poured from the bottle,
  - Spreading qualities of lotion (suspension forms) when it is applied to an affected area.

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- A suspending agent that is **thixotropic** as well as **pseudoplastic** proved to be useful,
- Such systems form a gel on standing and become fluid when disturbed.
- E.g. When bentonite and carboxymethylcellulose dispersions are mixed, the resulting curve shows both pseudoplastic and thixotropic characteristics.

Preparation of suspensions

- Factors to be considered:
  - Dose of the active drug (API)
  - Route of administration
  - Patient population
  - Physicochemical characteristics of the API
  - Biopharmaceutical properties of the API
  - The physical and chemical properties of the other components of the formulation

- Common excipients for preparation of suspensions:

Wetting agents	They are added to disperse solids in continuous liquid phase.
Flocculating agents	They are added to floc the drug particles
Thickeners	They are added to increase the viscosity of suspension.
Buffers and pH adjusting agents	They are added to stabilize the suspension to a desired pH range.
Osmotic agents	They are added to adjust osmotic pressure comparable to biological fluid.
Coloring agents	They are added to impart desired color to suspension and improve elegance.
Preservatives	They are added to prevent microbial growth.
External liquid vehicle	They are added to construct structure of the final suspension.

- **Suspending agents**
  - Suspending agent are also known as hydrophilic colloids which form colloidal dispersion with Water and increase the viscosity of the continuous phase.
  - Suspending agent form film around particle and decrease interparticle attraction.
  - Most suspending agents perform two functions:
    - Act as a suspending agent
    - Impart viscosity to the solution

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- Preferred suspending agents are those that give **thixotropy** to the media,

- List of suspending agents:

  - Alginates
  - Methylcellulose (MC)
  - Hydroxyethylcellulose (HEC)
  - Carboxymethylcellulose (CMC)
  - Sodium Carboxymethylcellulose
  - Microcrystalline cellulose (MCC)
  - Hydroxypropyl methylcellulose (HPMC)
  - Acacia
  - Tragacanth
  - Xantham gum
  - Bentonite
  - Carbomer
  - Carrageen
  - Powdered cellulose
  - Colloidal silicon dioxide
  - Gelatin

- **Wetting Agents**
  - Hydrophilic materials are easily wetted by water while hydrophobic materials are not.
  - The extent of wetting by water is dependent on the hydrophillicity of the materials.
  - The concentration used is less than 0.5 %.

- **Surfactants**
  - Surfactants decrease the interfacial tension.
  - Generally, we use non-ionic surfactants but ionic surfactants can also be used depending upon certain conditions.
  - Polysorbate 80 is most widely used due to its following advantages:
    - It is non-ionic so no change in pH of medium
    - No toxicity. Safe for internal use.

- **Hydrophilic Colloids**
  - Hydrophilic colloids coat hydrophobic drug particles in one or more than one layer.
  - This will provide hydrophillicity to drug particles and facilitate wetting.
  - They cause deflocculation of suspension because force of attraction is declined. e.g. acacia, tragacanth, alginates, guar gum.

- **Buffers**
  - Buffers are the materials which when dissolved in a solvent will resist any change in pH when an acid or base is added.
  - To encounter stability problems all liquid formulation should be formulated to an optimum pH.
  - Rheology, viscosity and other property are also dependent on the pH of the system.
  - Most commonly used buffers are salts of weak acids such as: carbonates, citrates, gluconates, phosphate and tartrates.

- **Osmotic Agents**

  - They are added to produce osmotic pressure comparable to biological fluids when suspension is to be intended for ophthalmic or injectable preparation.

  - Most commonly used osmotic agents are: dextrose, mannitol, sorbitol, sodium chloride, sodium sulfate, and glycerol.

- **Preservatives**
  - Naturally occurring suspending agents such as tragacanth, acacia, xanthan gum are susceptible to microbial contamination.
  - Commonly used preservatives: Propylene glycol, EDTA, Benzalkonium chloride, Benzoic acid, Butyl paraben.
  - This leads to:
    - loss in suspending activity of suspending agents,
    - loss of color, flavor and odor,
    - change in elegance etc.

- **Flavoring And Coloring Agents**
  - They are added to increase patient acceptance,
  - Commonly used colors:
    - Titanium dioxide (white)
    - Brilliant blue (blue)
    - Indigo carmine (blue)
    - Amaranth (red)
    - Tartarazine (yellow)
    - Annatto seeds (yellow to orange)

- **Sweetening Agents**
  - Bulk sweeteners
    - Sugars such as xylose, ribose, glucose, mannose.
    - Sugar alcohols such as sorbitol, xylitol, mannitol
  - Artificial sweetening agents
    - Sodium cyclamate
    - Sodium saccharin
    - Aspartame

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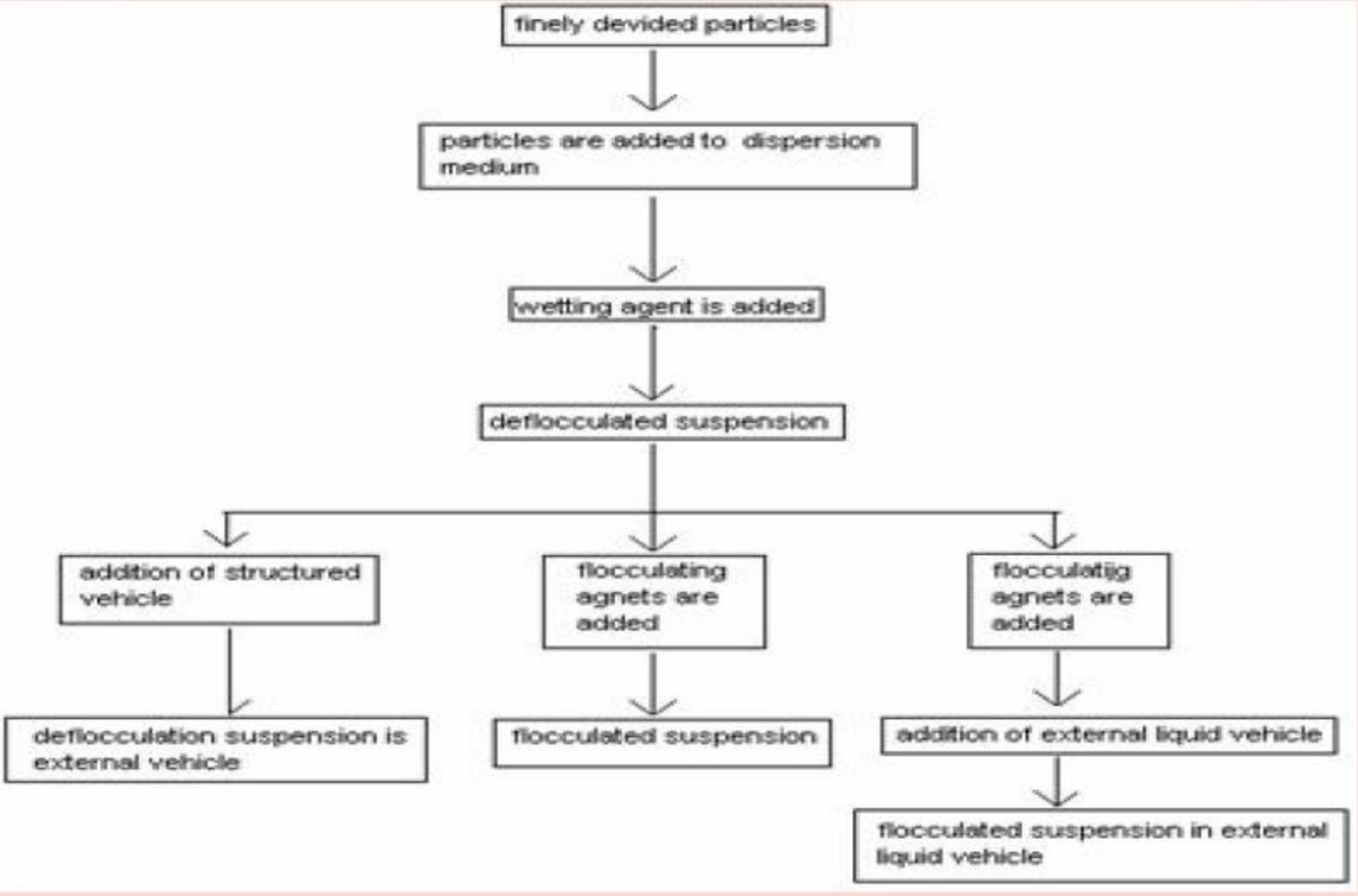
- **Antioxidants**
  - Ascorbic acid derivatives such as ascorbic acid, erythorbic acid,
  - Thiol derivatives such as thio glycerol, cytosine, acetylcysteine,
  - Tocopherols
  - Butylated hydroxy anisole(BHA)
  - Butylated hydroxytoluene (BHT)
  - Sodium bi sulfite,
  - Sodium sulfateacetone

- General method for preparation of suspensions:


finely devided particles
particles are added to dispersion medium
wetting agent is added
deflocculated suspension
addition of structured vehicle
flocculating agnets are added
flocculatijg agnets are added
deflocculation suspension is external vehicle
flocculated suspension
addition of external liquid vehicle
flocculated suspension in external liquid vehicle

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- The drug particles (dispersed phase) in a suspensions could be:
  - Diffusible solids (dispersible solids)
  - Indiffusible solids,
  - Poorly wettable solids

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- Small scale preparation of suspensions:

Step 1:

- Grinding/levigating the insoluble materials in the mortar to a smooth paste with a vehicle (containing dispersion stabilizer)

Step 2:

- All soluble ingredients are dissolved in some portion of the vehicle and added to the smooth paste to step1 to get slurry

Step 3:

- The slurry is transferred to a graduated cylinder, the mortar is rinsed with successive portion of the vehicle

Step 4:

- Decide whether the solids are:
  - Suspended in a structured vehicle (deflocculated suspension)
  - Flocculated
  - Flocculated and then suspended
- Add the vehicle containing the suspending agent (or) flocculating agent

Step 5:

- Make up the dispersion to the final volume
- Thus suspension is prepared

Label and Storage

- Read …

Evaluation of Suspensions

Physical Stability of Suspensions

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- The following methods are used to evaluate the physical stability of suspensions:
  - Sedimentation method
  - Rheological method
  - Electro kinetic method
  - Micromeritic method